

EDITORIAL COMMENT

Aldosterone Blockade in Metabolic Syndrome

Hitting the Target or Still Missing Some Links?*

Dominic Y. Leung, MBBS, PhD

Liverpool, New South Wales, Australia

Aldosterone blockade improves symptoms and outcomes in systolic heart failure and after acute myocardial infarction when added to angiotensin-converting enzyme inhibitors (ACEI) or angiotensin-receptor blockers (ARB). However, studies on the impact of aldosterone blockade on left ventricular (LV) volumes and ejection fraction have been inconsistent (1,2) with a meta-analysis of 19 randomized trials showing only a modest increase in LV ejection fraction of 3% despite an impressive 20% reduction in all-cause mortality (3). The beneficial effects of aldosterone blockade may be mediated by processes other than just reverse remodeling and improvement in ejection fraction.

See page 1239

Cardiac extracellular matrix (ECM) plays an active role in modulating cardiac function and undergoes extensive and continuous turnover as important steps in an injury-reparative process. Fibroblasts are the predominant cell types in the ECM and proliferation of cardiac fibroblasts in response to a wide range of injury leads to increased collagen synthesis resulting in cardiac fibrosis and dysfunction. By stimulating collagen synthesis, aldosterone promotes cardiac fibrosis, and attenuation of the excessive ECM turnover by aldosterone blockade has been suggested to be the mechanism underlying its beneficial effects in systolic heart failure (4,5). Furthermore, circulating biomarkers of collagen turnover provide a window to ECM

turnover. Because types I and III collagen are most abundant in the heart, the most studied biomarkers are the procollagen type III N-terminal propeptide (PIIINP) and procollagen type I C-terminal propeptide (PICP). Levels of these biomarkers have been shown to be of prognostic values in systolic heart failure (4,5) and aldosterone blockade led to a decrease in these biomarker levels. Moreover, the clinical benefits appeared to be most evident in patients with elevated biomarker levels (5).

The promise of aldosterone blockade in systolic heart failure has led to studies examining its use in other cardiac diseases characterized by increased cardiac fibrosis but without overt systolic dysfunction, including heart failure with preserved ejection fraction, hypertensive and diabetic heart disease, and chronic kidney disease (6–8). Metabolic syndrome is another such condition. Metabolic syndrome is a constellation of vascular risk factors of metabolic origin, and aldosterone is considered to be central in the pathophysiology (9).

In this issue of *JACC*, Kosmala et al. (10) examined the effects of spironolactone on LV structure, function, and serum levels of biomarkers of collagen synthesis (PICP, PIIINP, and transforming growth factor β_1) in patients with metabolic syndrome already on ACEI or ARB. Eighty patients were randomized to either spironolactone 25 mg/day or placebo. After 6 months, the spironolactone group had a significant decrease in PICP, PIIINP, and transforming growth factor β_1 levels, left atrial dimension, and LV wall thickness and mass. The treatment group had an improvement in LV mechanics evidenced by an increase in longitudinal strain and strain rate, E_m and a decrease in E/e' . A decrease in calibrated integrated backscatter in the basal posterior walls as a surrogate of fibrosis was also seen. More interestingly and perhaps more provocatively, there were differential responses ac-

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

From the Department of Cardiology, Liverpool Hospital, Liverpool, New South Wales, Australia; and the University of New South Wales, Sydney, Australia. Dr. Leung has reported that he has no relationships relevant to the contents of this paper to disclose. Jeroen J. Bax, MD, PhD, served as Guest Editor for this paper.

cording to the baseline PICP levels and LV function. Significant improvement was seen with spironolactone in the middle and upper tertiles of baseline PICP levels and in the lowest and middle tertiles of measures of LV function.

The study is important and timely. It further adds to the growing evidence for aldosterone blockade in “hyperfibrotic conditions” beyond systolic heart failure and post-acute myocardial infarction. Previous studies have demonstrated similar beneficial effects, albeit echocardiographic and biochemical ones, of aldosterone blockade in hypertension and diabetes, heart failure with preserved systolic function, and chronic kidney disease (6–8). This is the first study not only to extend the observation to metabolic syndrome, but also to provide possible mechanistic links between myocardial derangements, aldosterone blockade, and improvement in LV systolic and diastolic function. Myocardial derangements were evidenced by a higher LV end-diastolic dimension, LV mass index, left atrial dimension, E/e' , calibrated integrated backscatter and a lower E_m , and longitudinal strain and strain rate, associated with higher levels of PICP and PIIINP. Spironolactone treatment improved myocardial derangements and reduced biomarker levels. Subgroup analyses and multivariate models revealed that patients with higher collagen turnover and those with lower strain, strain rate, and E_m velocities benefited more from spironolactone. More importantly, the decrease in biomarker levels with spironolactone was more marked in patients with the most deranged myocardial mechanics. It may be inferred that: 1) patients with more cardiac fibrosis had the most deranged myocardial mechanics; 2) these patients benefited most from aldosterone blockade; and 3) reduction in cardiac fibrosis was the underlying mechanism of improvement with treatment. Another important observation is that these beneficial effects of spironolactone were seen in patients already treated with either ACEI or ARB. Both angiotensin II and aldosterone stimulate cardiac fibrosis and additional blockade of the renin-angiotensin-aldosterone system with spironolactone to cover “aldosterone escape” allows further suppression of cardiac fibrosis.

Are circulating levels of collagen turnover indicative of the degree of cardiac fibrosis? Perhaps more importantly, is any decrease in biomarker levels with aldosterone blockade associated with a parallel decrease in cardiac fibrosis? Collagen is the most abundant protein in the body with a highly dynamic turnover. Biomarkers of collagen turnover are not

cardiac-specific and high levels may not necessarily reflect changes at the microscopic level in the myocardium. Evidence for such pathophysiological link is far from conclusive. A multitude of biomarkers are available: biomarkers related to collagen synthesis (PICP and PIIINP) and biomarkers related to collagen degradation (matrix metalloproteinases and tissue inhibitors of metalloproteinases). There is no common consensus on which ones are the most preferable. Furthermore, factors relating to the demographics of the subjects, the methods of immunoassay, presence of comorbidities, and the elimination of the circulating biomarkers may all potentially confound the measurement and interpretation of biomarker levels (11). Therefore, demonstrating a direct connection between circulating levels of biomarkers, the status of the myocardial collagen network, and the alteration in myocardium structure and function is still an all-important missing link.

The number of patients in the study was small, and the study was powered according to a difference in peak strain between the 2 groups. Further subgroup analyses on differential benefits according to baseline strain values or biomarker levels were post hoc, involved even smaller number of patients, and tests for interaction were not reported. Nevertheless, the findings on subgroup analysis should be considered hypothesis-generating, and they are definitely worth further investigations.

A most important missing link is if echocardiographic and biochemical beneficial effects seen with spironolactone in metabolic syndrome would equate to an improvement in symptoms and patient outcome. Large randomized trials of ACEI and ARB in heart failure and preserved ejection fraction failed to show any significant clinical benefits. Would the fall in biomarkers of collagen turnover; increase in strain, strain rate, and E_m ; or other changes in echocardiographic parameters seen in this study lead to improvement in symptoms and patient outcomes in metabolic syndrome? Whereas tissue velocities, myocardial deformation, and tissue characterization measure true intrinsic myocardial properties, it remains to be shown that the improvement of the degree seen in this study will lead to improvement in symptoms and clinical outcome. The lack of information on functional status and outcome data in the current study precludes drawing any such conclusions. The link between reduction in biomarker levels with improved ventricular mechanics and improvement in symptoms and prognosis in metabolic syndrome is still elusive.

A more philosophical question is about the effect of life-style changes, in contrast/in addition to aldosterone blockade, on myocardial mechanics and biomarker levels. Through no faults of the investigators, there were no meaningful changes in the biochemical and morphometric profiles of the patients after 6 months of monitoring and treatment. Perhaps it is more important to focus on the root of the problems in metabolic syndrome in addition to just targeting the biochemical mediators.

This study by Kosmala et al. (10) is unique in that it provides evidence for beneficial effects of aldosterone blockade in metabolic syndrome, which, in addition to hypertensive heart disease, chronic kidney diseases, heart failure with preserved systolic function, is certainly another target for more comprehensive blockade of the renin-angiotensin-aldosterone system. Given the increas-

ing prevalence of metabolic syndrome, the inability to adopt sufficient life-style modifications and the significant morbidities and mortality associated with the condition, the medical community is in need of potentially “disease modifying” therapies such as aldosterone blockade. The missing links notwithstanding, we welcome studies by Kosmala et al. (10) and await the results of large-scale clinical trials such as TOPCAT (Treatment of Preserved Cardiac function heart failure with an Aldosterone antagonist) of aldosterone blockade in “hyperfibrotic” conditions with interests.

Reprint requests and correspondence: Prof. Dominic Y. Leung, Department of Cardiology, Liverpool Hospital, Locked Bag, 7103, Liverpool BC, NSW 1871, Australia. E-mail: d.leung@unsw.edu.au.

REFERENCES

- Udelson JE, Feldman AM, Greenberg B, et al. Randomized, double-blind, multicenter, placebo-controlled study evaluating the effect of aldosterone antagonism with eplerenone on ventricular remodeling in patients with mild-to-moderate heart failure and left ventricular systolic dysfunction. *Circ Heart Fail* 2010;3:347-53.
- Chan AK, Sanderson JE, Wang T, et al. Aldosterone receptor antagonism induces reverse remodeling when added to angiotensin receptor blockade in chronic heart failure. *J Am Coll Cardiol* 2007;50:591-6.
- Ezekowitz JA, McAlister FA. Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials. *Eur Heart J* 2009;30:469-77.
- Zannad F, Alla F, Dousset B, Perez A, Pitt B. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: insights from the Randomized Aldactone Evaluation Study (RALES). *RALES Investigators. Circulation* 2000;102:2700-6.
- Iraqi W, Rossignol P, Angioi M, et al. Extracellular cardiac matrix biomarkers in patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure: insights from the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) study. *Circulation* 2009;119:2471-9.
- Edwards NC, Ferro CJ, Kirkwood H, et al. Effect of spironolactone on left ventricular systolic and diastolic function in patients with early stage chronic kidney disease. *Am J Cardiol* 2010;106:1505-11.
- Mak GJ, Ledwidge MT, Watson CJ, et al. Natural history of markers of collagen turnover in patients with early diastolic dysfunction and impact of eplerenone. *J Am Coll Cardiol* 2009;54:1674-82.
- Mottram PM, Haluska B, Leano R, Cowley D, Stowasser M, Marwick TH. Effect of aldosterone antagonism on myocardial dysfunction in hypertensive patients with diastolic heart failure. *Circulation* 2004;110:558-65.
- Sowers JR, Whaley-Connell A, Epstein M. Narrative review: the emerging clinical implications of the role of aldosterone in the metabolic syndrome and resistant hypertension. *Ann Intern Med* 2009;150:776-83.
- Kosmala W, Przewlocka-Kosmala M, Szczepanik-Osadnik H, Mysiak A, O'Moore-Sullivan T, Marwick TH. A randomized study of the beneficial effects of aldosterone antagonism on LV function, structure, and fibrosis markers in metabolic syndrome. *J Am Coll Cardiol* 2011;4:1239-49.
- Lopez B, Gonzalez A, Diez J. Circulating biomarkers of collagen metabolism in cardiac diseases. *Circulation* 2010;121:1645-54.

Key Words: angiotensin-converting enzyme ■ angiotensin-receptor blocker ■ extracellular matrix ■ left ventricular.